National Cancer Institute

Successful Coordination of Multi-site Investigator-Sponsor Clinical Trials

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Agenda

- Investigator-Sponsor responsibilities
- Multi-site clinical trial coordination

Sponsor-Investigator

- Individual who serves as a sponsor-investigator
- Fulfill the obligations of both the sponsor and the investigator
- Initiates and conducts the investigation

Transfer of Sponsor Responsibilities

- May transfer responsibilities to a Contract Research Organization (CRO)
  - Design of a protocol
  - Selection of investigators
  - Monitoring
  - Preparation of materials for FDA submission
- Needs to be in writing
- CRO then assumes the responsibilities of the sponsor

Investigational New Drug (IND) Application

- Sponsor submits to the FDA
- Descriptive notification of intention to conduct clinical studies with an investigational drug or biologic
- Allows for transportation of product (non-approved drug) across state lines

Content and Format of an IND…

- Cover Letter/Memo
- Cover sheet (FDA Form 1571)
- Statement of Investigator Statement (FDA Form 1572)
- Certificate of Compliance (Form 3674)
- Table of contents
- Introductory statement and general investigational plan

…Content and Format of an IND

- Chemistry, manufacturing and controls (CMC)*
- Pharmacology and Toxicology*
- Investigator's brochure (IB)
- Clinical Protocols
- Summary of previous human experience with the investigational drug
- Additional information
- FDA checklist

* *Letter of Authorization for Investigator-Sponsor*

FDA Form 1571 page 1

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(Title 21, Code of Federal Regulations (CFR) Part 312)

Form Approved: OMB No. 0910-0014
Expiration Date: April 30, 2015
See PRA Statement on page 3.

NOTE: No drug/biologic may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. Name of Sponsor

2. Date of Submission *(mm/dd/yyyy)*

3. Sponsor Address

Address 1 *(Street address, P.O. box, company name c/o)*

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City | State/Province/Region

Country | ZIP or Postal Code

4. Telephone Number *(Include country code if applicable and area code)*

5. Name(s) of Drug *(Include all available names: Trade, Generic, Chemical, or Code)*

Continuation Page for #5

6. IND Number *(If previously assigned)*

7. (Proposed) Indication for Use

Is this indication for a rare disease (prevalence <200,000 in U.S.)? ☐ Yes ☐ No

Does this product have an FDA Orphan Designation for this indication? ☐ Yes ☐ No

If yes, provide the Orphan Designation number for this indication:

Continuation Page for #7

8. Phase(s) of Clinical Investigation to be conducted ☐ Phase 1 ☐ Phase 2 ☐ Phase 3 ☐ Other *(Specify)*:

9. List numbers of all Investigational New Drug Applications (21 CFR Part 312), New Drug Applications (21 CFR Part 314) , Drug Master Files (21 CFR Part 314.420) , and Biologics License Applications (21 CFR Part 601) referred to in this application.

10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted..

Serial Number _____

11. This submission contains the following *(Select all that apply)*

☐ Initial Investigational New Drug Application (IND)
☐ Response to Clinical Hold
☐ Response To FDA Request For Information
☐ Request For Reactivation Or Reinstatement
☐ Annual Report
☐ General Correspondence
☐ Development Safety Update Report (DSUR)
☐ Other *(Specify)*:

Protocol Amendment(s)
☐ New Protocol
☐ Change in Protocol
☐ New Investigator
☐ PMR/PMC Protocol

Information Amendment(s)
☐ Chemistry/Microbiology
☐ Pharmacology/Toxicology
☐ Clinical ☐ Statistics
☐ Clinical Pharmacology

Request for
☐ Meeting
☐ Proprietary Name Review
☐ Special Protocol Assessment
☐ Formal Dispute Resolution

IND Safety Report(s)
☐ Initial Written Report
☐ Follow-up to a Written Report

12. Select the following only if applicable. *(Justification statement must be submitted with application for any items selected below. Refer to the cited CFR section for further information.)*

☐ Emergency Research Exception From Informed Consent Requirements, 21 CFR 312.23 (f)
☐ Charge Request, 21 CFR 312.8

Expanded Access Use, 21 CFR 312.300

☐ Individual Patient, Non-Emergency 21 CFR 312.310
☐ Individual Patient, Emergency 21 CFR 312.310(d)
☐ Intermediate Size Patient Population, 21 CFR 312.315
☐ Treatment IND or Protocol, 21 CFR 312.320

For FDA Use Only

CBER/DCC Receipt Stamp | DDR Receipt Stamp | Division Assignment

IND Number Assigned

FDA Form 1571 page 2

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13. Contents of Application – This application contains the following items *(Select all that apply)*

- ☐ 1. Form FDA 1571 *(21 CFR 312.23(a)(1))*
- ☐ 2. Table of Contents *(21 CFR 312.23(a)(2))*
- ☐ 3. Introductory statement *(21 CFR 312.23(a)(3))*
- ☐ 4. General Investigational plan *(21 CFR 312.23(a)(3))*
- ☐ 5. Investigator's brochure *(21 CFR 312.23(a)(5))*
- ☐ 6. Protocol(s) *(21 CFR 312.23(a)(6))*
  - ☐ a. Study protocol(s) *(21 CFR 312.23(a)(6))*
  - ☐ b. Investigator data *(21 CFR 312.23(a)(6)(iii)(b))* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *(21 CFR 312.23(a)(6)(iii)(b))* or completed Form(s) FDA 1572
- ☐ 6. Protocol(s) *(Continued)*
  - ☐ d. Institutional Review Board data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *(21 CFR 312.23(a)(7))*
  - ☐ Environmental assessment or claim for exclusion *(21 CFR 312.23(a)(7)(iv)(e))*
- ☐ 8. Pharmacology and toxicology data (21 CFR 312.23(a)(8))
- ☐ 9. Previous human experience *(21 CFR 312.23(a)(9))*
- ☐ 10. Additional information *(21 CFR 312.23(a)(10))*
- ☐ 11. Biosimilar User Fee Cover Sheet *(Form FDA 3792)*
- ☐ 12. Clinical Trials Certification of Compliance *(Form FDA 3674)*

14. Is any part of the clinical study to be conducted by a contract research organization? ☐ Yes ☐ No

If Yes, will any sponsor obligations be transferred to the contract research organization? ☐ Yes ☐ No

If Yes, provide a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred *(use continuation page)*.

Continuation Page for #14

15. Name and Title of the person responsible for monitoring the conduct and progress of the clinical investigations

16. Name(s) and Title(s) of the person(s) responsible for review and evaluation of information relevant to the safety of the drug

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold or financial hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

17. Name of Sponsor or Sponsor's Authorized Representative

18. Telephone Number *(Include country code if applicable and area code)*

19. Facsimile (FAX) Number *(Include country code if applicable and area code)*

20. Address

Address 1 *(Street address, P.O. box, company name c/o)*

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City | State/Province/Region

Country | ZIP or Postal Code

21. Email Address

22. Date of Sponsor's Signature *(mm/dd/yyyy)*

23. Name of Countersigner

24. Address of Countersigner

Address 1 *(Street address, P.O. box, company name c/o)*

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City | State/Province/Region

Country: United States of America | ZIP or Postal Code

WARNING : A willfully false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).

25. Signature of Sponsor or Sponsor's Authorized Representative

26. Signature of Countersigner

Submission Requirements: General

- Gather all components of the application
  - Use 8 1/2 x 11 paper
  - 3 hole punched left side
- Paginate submissions within each section
- Create tabs using 2 sets of 5-tab dividers
- Create a cover memo
- Ensure that all signatures have been obtained
- Make 3 copies & CD:
  - 2 to send to FDA
  - 1 for Sponsor records

Submission Requirements: Supplies

- Order supplies through your Administrative Officer (AO) or Purchasing Officer:
  - Paginate submissions within each section
  - Avery 2x4 labels, item 8163
  - Avery 5-tab dividers, item 11446
  - ACCO prong fasteners, 3 ½ inch, item 70724
  - 3-hole paper
  - Binders
  - FedEx medium and large boxes, envelopes, and plastic label envelopes

Submission Requirements: Binders

CDER

- Binders
  - Red (FDA Form 2575) – Archive
  - Green (FDA Form 2675a – Chemistry
  - Orange (FDA Form 2675b) – Microbiology
  - U.S. Government Printing Office (GPO)
    (202) 512-1800
- FDA/CDER
  Central Document Room
  5901-B Ammendale Rd.
  Beltsville, MD 20705-1266
  301-210-2880

CBER

- Binders
  - Gray (25074 or 81522) – Archive
  - Red (25079 or 81752) – 1st Review
  - Tangerine/Orange (25977/81652) – 2nd and additional review copies
- FDA/CDER
  Therapeutic Biological Products Document Room
  5901-B Ammendale Road
  Beltsville, MD 20705-1266
  301-210-2880

Submission Requirements: Label

Investigational New Drug Application, **IND# XXXXXX**
Serial #00XX
Enter Date

DRUG NAME
PI NAME, M.D.
Dept Name, IC
Volume 1 of 1 – IND Archive Original

List total number of binders required to hold ONE copy here

Change Name to "Chemistry" Or "Microbiology"

Types of IND Amendments

- Protocol Amendments
  - New Protocol, change in protocol, new investigator
- Information Amendments
- IND Safety Reports
  - Serious and unexpected clinical adverse event or laboratory finding affecting safety
  - Fatal or life threatening within 7 days, 15 days for others
- Annual Reports
  - Must be submitted within 60 days of the anniversary of when IND went into effect
  - See the regulation for content and format

IND Status

- Pending
- Active
- Clinical Hold
  - Partial Hold

Clinical Responsibilities

- Select qualified investigators and monitors
- Provide Investigators with needed information
- Ensure study conducted in accordance with Investigational Plan
- Ensure investigation is properly monitored
- Promptly report adverse events and new risks to FDA and all investigators
- Maintain adequate records
- Record keeping and record retention
- Ensuring the return or disposition of unused investigational drug supplies

Investigator Selection

- Assess qualification of PI and Sub-investigators
  - Qualified by training & experience
  - Ability to supervise administration of product
  - Investigational Product shipped to them
- Assess site (physical plant capabilities).
  - Is there adequate pharmacy space for drug storage?
  - Are there SOPs for freezer alarms?

Monitoring of Clinical Trials

- Monitoring is necessary to assure that the:
  - rights and safety of human subjects are protected
  - reported trial data are accurate, complete, and verifiable from source documents
  - conduct of trial is in compliance with protocol, good clinical practice (GCP) and applicable regulatory requirements.
- Sponsor must have written monitoring procedures (SOPs) to assure the quality of the study and ensure that each person involved carries out their duties

Monitor Selection

- Monitor the progress of the investigation
- Monitoring function may be performed by:
  - The sponsor
  - Contract staff
- Select a monitor qualified by training and experience
  - Clinical Research Associate (CRA)

Sponsor Site Visits

- Several types of site visits conducted by the sponsor
  - Pre-study qualification visit
  - Initiation visit
  - Monitoring visit
  - Close-out visit

Potential Actions for Non-compliance

- Secure compliance

  OR
- Stop product shipments to the investigator
- Terminate the investigator's participation in the study
- Secure return or disposal of investigational product

Recordkeeping and Record

- Regulatory file/binder
- Drug Accountability
- Financial interests
- Records and reports
  - 2 years after a marketing application is approved for the drug
  - If application is not approved for the drug, 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified

Withdrawal of IND

- Can do so at any time prejudice
- FDA shall be so notified
- All clinical investigations conducted under the IND shall be ended
- All current investigators notified
- All stocks of the drug returned to the sponsor or otherwise disposed of
- If withdrawn for safety, sponsor shall promptly inform FDA, all participating investigators, and all reviewing IRBs with reason

FDA Resources

Development & Approval Process (Drugs)

- How Drugs are Developed and Approved
- Types of Applications
- Investigational New Drug (IND) Application
- Emergency Investigational New Drug (EIND) Applications for Antiviral Products
- IND Forms and Instructions
- **Investigator-Initiated Investigational New Drug (IND) Applications**
- Pre-IND Consultation Program
- Regulatory Information for INDs

Investigator-Initiated Investigational New Drug (IND) Applications

This table provides links to information for investigators about submitting Investigational New Drug (IND) applications to FDA. The resources for application reporting and applications procedures apply to IND applications for both clinical research and clinical treatment.

IND Applications for Clinical Investigations (*Product Development*)	IND Application Reporting	IND Application Procedures	IND Applications for Clinical Treatment (*Expanded Access*)
Overview	Overview	Overview	Overview
Contents and Format	Protocol Amendments	Exemptions from IND Requirements	Contents and Format
Regulatory and Administrative Components	Information Amendments	Interactions with FDA	Treatment of a Single Patient in Emergency Setting
Non-clinical Components	Safety Reports	Clinical Hold	Treatment of a Single Patient in Non-emergency Setting
Clinical Components	Annual Reports	Investigator's Responsibilities	Treatment of a Group of Patients

Establish a Team

- Plan/organize the study
- Recruit participating sites
- Oversee aspects of the study
- Perform data analysis
- Write study reports and/or papers
- Consider separating Sponsor activities from Investigator activities when developing a team(s)

Determine Trial Feasibility

- Estimate trial cost
- Evaluate availability of participants and/or investigators
- Determine what agreements will be needed
- Adequate staff to serve as the coordinating center
- Authorship considerations
- Registration process
- If applicable, randomization/blinding processes

IRB Authorization Agreement (IAA)

- Two or more *federally-assured* institutions collaborate on human subjects research supported by a Common Rule agency, the institutions may rely on a single IRB (an "IRB of Record") for review and continuing oversight of the research, in order avoid duplicate review
- May cover a single study or a group of studies
- AKA: Reliance Agreement

Regulatory Support for IRB of Record

OHRP (45 CFR 46.11)

"Cooperative research projects are those projects…which involve more than one institution. …[An] institution participating in a cooperative project may enter into a **joint review arrangement**, **rely upon the review of another qualified IRB**, or make **similar arrangements** for avoiding duplication of effort."

FDA (21 CFR 56.114)

"…institutions involved in multi-institutional studies may use **joint review**, **reliance upon the review of another qualified IRB**, or **similar arrangements** aimed at avoidance of duplication of effort."

IAA Requirements

- Minimum requirements:
  - Title of the study (or studies)
  - Names of the investigators and institutional officials at each institution
  - Rights and responsibilities of each institution with regard to human subject research protections
- Copies of the signed agreement must be kept at both institutions and be made available to any Common Rule agency upon request

IAA: OHRP Template

Version Date: 03/31/2011

Sample text for an Institution with a Federalwide Assurance (FWA) to rely on the IRB/IEC of another institution (institutions may use this sample as a guide to develop their own agreement).

Institutional Review Board (IRB) Authorization Agreement

Name of Institution or Organization Providing IRB Review (Institution/Organization A):

_____

IRB Registration #: _____ Federalwide Assurance (FWA) #, if any: _____

Name of Institution Relying on the Designated IRB (Institution B):

_____

FWA #: _____

The Officials signing below agree that ___(*name of Institution B)*___ may rely on the designated IRB for review and continuing oversight of its human subjects research described below: (*check one*)

(___) This agreement applies to all human subjects research covered by Institution B's FWA.

(___) This agreement is limited to the following specific protocol(s):

Name of Research Project:_____
Name of Principal Investigator:_____
Sponsor or Funding Agency: _____ Award Number, if any: _____

(___) Other (*describe*):_____

The review performed by the designated IRB will meet the human subject protection requirements of Institution B's OHRP-approved FWA. The IRB at Institution/Organization A will follow written procedures for reporting its findings and actions to appropriate officials at Institution B. Relevant minutes of IRB meetings will be made available to Institution B upon request. Institution B remains responsible for ensuring compliance with the IRB's determinations and with the Terms of its OHRP-approved FWA. This document must be kept on file by both parties and provided to OHRP upon request.

Signature of Signatory Official (Institution/Organization A):
_____ Date: _____

Print Full Name: _____ Institutional Title: _____

NOTE: The IRB of Institution A may need to be designated on the OHRP-approved FWA for Institution B.

Signature of Signatory Official (Institution B):
_____ Date: _____

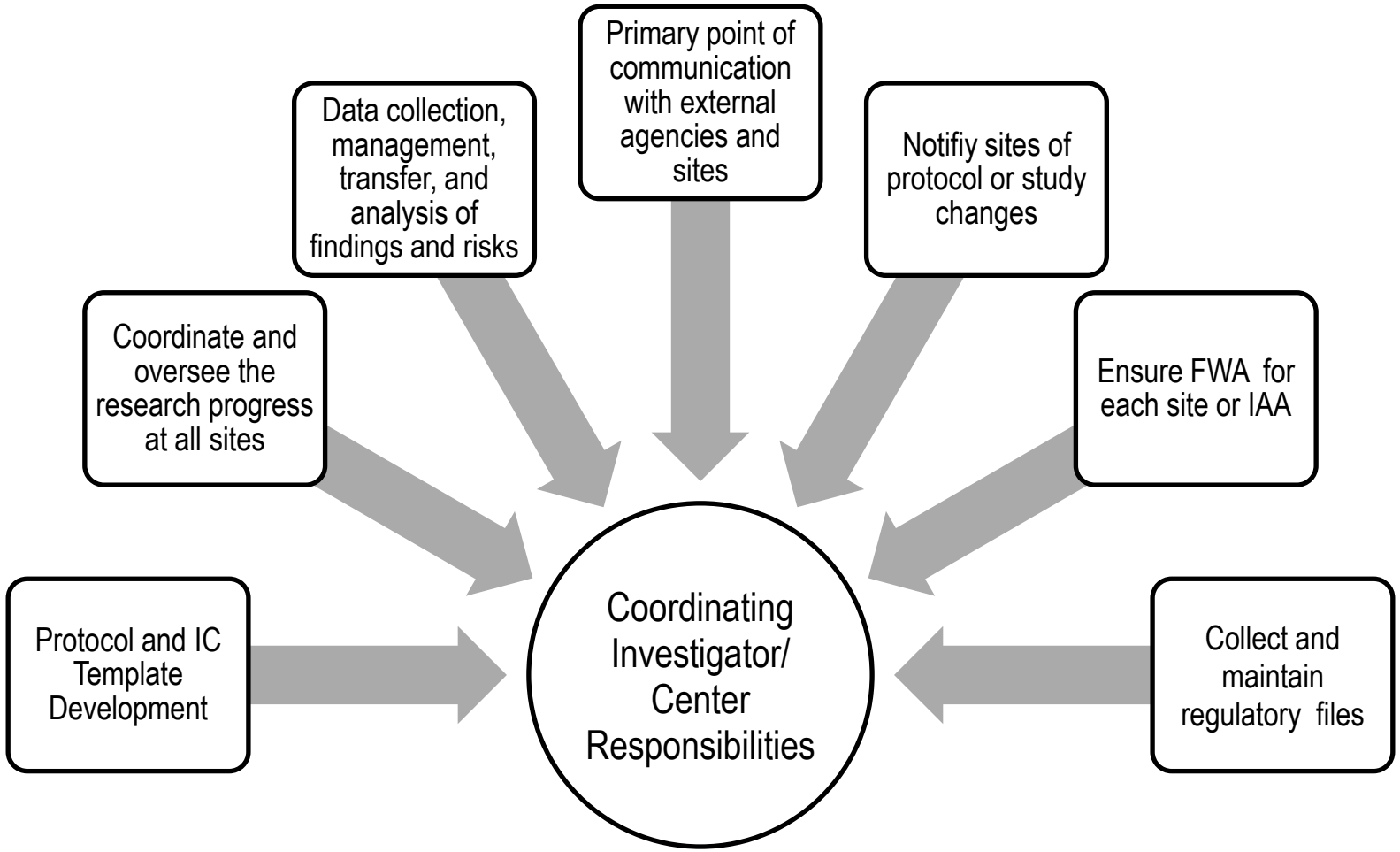
Print Full Name: _____ Institutional Title: _____

http://www.hhs.gov/ohrp/assurances/forms/irbauthorizpdf.pdf

NIH IRP Process

- Online form for one additional site
- For 2 or more participating sites, contact the Office of Human Subjects Research Protections
  - 301-402-3444
  - Shirley Rojas
    Health Science Policy Analyst

PI/Coordinating Center Responsibilities



Protocol Development

- Design and develop protocol and model IC document for use at each participating site
- If using an IAA:
  - Consider how local context will be evaluated
- If not using IAA:
  - Ensure each protocol is reviewed and approved by the participating site's IRB prior to enrollment of subjects at that site
  - Maintain documentation of all participating site's IRB approvals

Study Coordination…

- Ensure that affiliated sites are using the correct version of the protocol and consent document
- Track subject enrollment
- Ensure informed consent is obtained and documented from each
- Track, report and maintain documentation of all serious adverse events and unanticipated problems and disseminate the information to participating sites

…Study Coordination

- Ensure drug accountability at all sites
  - Know who is supplying the study drug and how to order and store
- Register trial with clinicaltrials.gov

Communication

- Identify all key participant site staff and their roles
  - Reinforce use of delegation of authority log
  - Determine plan for regular communication with the external sites and how will this be documented
- Provide periodic updates to affiliated investigators on subject enrollment, general study progress, and relevant scientific advances

Clinical Data Management

- Determine how data will be collected: paper or electronic
- Develop CRFs
- Develop CRF instruction manual or incorporate into a Manual of Procedures (MOP)
- Store and/or manage data
- Data analysis processes
- Protect confidentiality of data

Document Management

- Collect and maintain critical documents from participating investigators, e.g. resume/CV, medical license, certification of completion of training, laboratory certifications and laboratory norms, signed COI disclosure forms

Protocol-specific Training

- All key study personnel and staff are trained on the conduct of the protocol and study procedures at all sites
- Communicate and document important announcements with all sites

Data and Safety Monitoring Plan

- Set up procedures to review performance at all sites
  - Recruitment, data collection, protocol adherence, regulatory requirements
- Determine the nature and frequency of site monitoring
  - Base decision on complexity and risk level of trial
- Identify what will be monitored
  - Consider plans for remediation and adjustment
- Select site monitor (s)

Summary and Questions

- Protocol and model IC document development
- Participating site selection
- Agreements
  - IRB of record
- Central data and document collection
  - CRF development
- Safety/event reporting to IRB and FDA
- Monitoring/auditing plan

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